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Arrhythmias

GENETIC FACTORS UNDERLYING VARIABILITY IN METHADONE PLASMA LEVELS AND QTC PROLONGATION DURING METHADONE TREATMENT FOR OPIOID ADDICTION: THE MEMORIES TRIAL

ACC Moderated Poster Contributions
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Background: Methadone-associated sudden death (SD) rose 468% between 1997-2005, becoming a leading public health issue. Methadone therapeutic response and cardiovascular risk are highly variable, due in-part to genetic factors. Respiratory depression and polymorphic ventricular tachycardia are the principal mechanisms of SD and likely relate to variable plasma levels and to variable QT prolongation associated with delayed potassium rectifier current (HeRG channel) inhibition, respectively.

Methods: We studied methadone day 1 peak plasma levels (before dose adjustments) and change (Δ) in QTc from pre-drug baseline to 21 days on therapy associated with rs104564 in the ABCB1 gene, which encodes the p-glycoprotein transporter, and rs12143842 in NOS1AP, the nitric oxide synthase 1 adaptor protein gene, previously associated with QT prolongation. Blood sample from 30 consecutive consenting participants initiating methadone for opioid addiction were drawn at baseline (to ensure methadone abstinence) and day 1 peak (4 hours). Genotyping employed Taqman real-time PCR.

Results: Mean plasma S-methadone was higher for ABCB1 CC versus non-CC genotypes (77.9 ng/mL vs. 57.3 ng/mL, p=0.046) as was dose-adjusted plasma level (peak level/dose; 2.65 vs. 1.96, p=0.043). Of 25 participants with complete data, 17 experienced ΔQTc prolongation (mean, 39.9 msec). For the entire sample the mean/median ΔQTc was 23.6 msec/15 msec. The ABCB1 CC genotype was more frequent for participants with ΔQTc above the median (61.5%) versus those below the median (16.7%, p=0.041), with a trend toward increased peak plasma levels above the median (71.0 ng/mL vs. 59.7 ng/mL (p=0.179). QTc prolongation was significantly associated with rs12143842 T allele frequency (45.8% above the ΔQTc median, 10.0% below, p=0.018).

Conclusions: In this study, plasma levels of S-methadone were affected by ABCB1 rs104564 genotype, and QTc prolongation was significantly associated with NOS1AP variant allele carriage and possibly with plasma S-methadone levels. With further study, these provocative findings relevant to methadone toxicity and proarrhythmia may lead to more personalized methadone dosing and safety.